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Pathogenesis of Insulin Resistance

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Abstract

Insulin resistance is interpreted as being a normal or raised insulin level giving rise to a biological reaction which is attenuated in effect; classically this cites to the weakened sensitivity to the disposal of insulin arbitrate glucose. *Compensatory hyperinsulinemia* eventuates when the secretion of the β cells of pancreas gets elevated to sustain the level of blood glucose in normal levels. The term *insulin resistance syndrome* is used to refer to a group of abnormalities and interconnected physical consequences that eventuate in long-standing insulin-resistant persons. Under standard situations of insulin reactivity, the response of insulin triggers the intake of glucose into the body cells, for utilization as energy, and impedes the utilization of fat for energy, as a result of which, the concentration of glucose circulating in the blood decreases. There are a number of risk factors for insulin resistance. Four major metabolic abnormalities characterize type 2 diabetes mellitus (T2DM): impaired insulin action, obesity, increased endogenous glucose output, and insulin secretory dysfunction. The evolution (and subsequent progression) of type 2 diabetes mellitus is delineated by a gradual deterioration of glucose tolerance over several years. Glucose tolerance testing, hyperinsulinemic euglycemic clamp, modified insulin suppression test, homeostatic model assessment (HOMA), and quantitative insulin sensitivity check index (QUICKI) method for insulin assessment are some of the methods by which insulin resistance can be measured. Moreover, longer-term effective researches as well are essential to preferably ascertain the significance of the glycemic index in the blood glucose regulation and to prevent the complications of diabetes, particularly in relations to insulin resistance risk factors. The possible role of insulin resistance in the glycemic index in depleting oxidative stress postprandially and related pro-inflammatory situations also merits further appraisal.

Keywords: insulin resistance, compensatory hyperinsulinemia, type 2 diabetes mellitus, obesity

1. Introduction

One of the most renowned hormones of our body is insulin which enables glucose to go inside the cells which additionally decreases blood glucose. The hormone insulin is secreted by the pancreas in response to glucose entering the bloodstream after a meal. Insulin resistance (IR) is contemplated as a pathological situation in which our body cells decline to react normally to insulin hormone [1]. To avert hyperglycemia and apparent damage to our body organs in the future [2], insulin production by the body starts when glucose enters into the bloodstream, predominantly from the dietary carbohydrate digestion and absorption. Under

standard situations of insulin reactivity, the response of insulin triggers the intake of glucose into the body cells, for utilization as energy, and impedes the utilization of fat for energy, as a result of which, the concentration of glucose circulating in the blood decreases, which results in glucose remaining within the normal range in case of consumption of a substantial amount of carbohydrates. Carbohydrates contains sugars, i.e., from only one glucose containing monosaccharides, such as fructose and glucose; two glucose containing disaccharides, like cane sugar; and many glucose containing polysaccharides (e.g., starches) and glycoprotein, glycolipids, etc. Fructose, ultimately metabolized into triglycerides inside the liver, stimulates the production of insulin and is seen to have a more impressive sequel than other carbohydrates. A customarily increased intake of carbohydrates, and specifically fructose, imparts to insulin resistance and has been connected to gain of weight and obesity [3–5]. If surplus blood glucose is not adequately transported into the cells even in the insulin's presence, the augmented level of blood glucose can elicit in the classic hyperglycemic triad of polydipsia (increased thirst), polyphagia (increased appetite), and polyuria (increased urination). Circumventing carbohydrates, a zero-carbohydrate diet or conditions of fasting can counteract insulin resistance [6, 7]. The first narration of insulin resistance is found historically in the 1960s, soon after the invention of radioimmunoassays helped in making serum insulin quantification possible and subsequently revealed that people having late-onset diabetes mellitus had high levels of insulin [8, 9]. Drs. Yalow and Berson [8, 9] defined insulin resistance as "a state in which a greater than normal amount of insulin is required to elicit a quantitatively normal response." The next milestone discovery in this context was the detection and ascertaining of the insulin receptor and also the discovery that insulin resistance led to hyperinsulinemia and the fact that this was interconnected very much with atypical/unconventional binding of insulin hormone with its receptor in various rodent models [10, 11]. The succeeding milestone discovery in the history of insulin resistance came with the pioneering recognition of the receptor for insulin and the observation that high insulin in blood, secondary to the insulin resistance, was interconnected with atypical binding of insulin hormone to its receptor [10, 11]. It was not before the year 1976 when the evidence came that defects in receptor for insulin could be interlinked with resistance to the insulin hormone in humans, provided genetic translational verification for the significance of insulin resistance [10]. Researchers like Kahn et al. [10] delineated two syndromes that were distinguished by virilization, acanthosis nigricans, hirsutism, anovulation, acne, and flawed binding of insulin on the insulin receptor of lymphocytes circulating in the blood. This initial syndrome was designated as type A insulin resistance when it took place without the existence of anti-insulin antibodies and the corresponding accountability of the insulin receptor was the main factor, and in contrast it was designated as the type B when it occurred with the clinical characteristics of various autoimmune ailments and it always occurred when neutralizing anti-insulin antibodies were present [10]. After this specification of type A and type B syndrome, all rare and extreme levels of insulin resistance like acanthosis nigricans syndrome, hyperandrogenism, the Rabson-Mendenhall syndrome, lipodystrophy, and leprechaunism were discovered [12, 13]. To defend the idea by Himsworth that some cases of diabetes were not secondary to absolute insulin deficiency, it was imperative to prove the truth that insulin circulating in the blood was present in the insensitive form in those patients as classified by Himsworth. This was put to rest with the publication by Yalow and Berson in 1960 of an immunoassay research of endogenous blood insulin in humans. During this novel innovative work, Berson and Yalow delineated an excellent immunological technique for measuring the amount of insulin that integrated the degree of specificity with sensitivity required to take the measurement of even the smallest

concentrations of insulin contained in the body circulation. Utilizing this novel technique to categorize immunoreactive insulin amounts present in plasma in normal people to those particular patients having maturity-onset type diabetes, it was conceived that the amounts of insulin were on the average elevated in the patients with diabetes. Putting stress on the rationale of these particular outcomes, both of them summarized that the tissues of a person with maturity-onset diabetes do not have a good response to the level of insulin; on the contrary, the tissues of a nondiabetic person respond very well to his level of insulin. In the words or terminology of Himsworth, patients with this character in diabetes can be considered as "insulin insensitive." In spite of the fact these results of the novel publication by Yalow and Berson were afterwards authenticated by various research groups, it became evident that the interconnection between insulin concentrations and plasma glucose in patients having type 2 diabetes was not such a simple one. To be precise, in a person with comparatively slight increments of fasting plasma glucose concentration, the responses of plasma insulin to oral glucose were equivalent or prominently higher than the normal but with elevated proportions of glucose intolerance and with the appearance of noteworthy hyperglycemia during fasting [14–17]. It was obligatory to evolve an exploratory perspective that would quantify in an unequivocal way the capability of an individual person to get rid of fixed glucose load under the influence of identical insulin stimuli during steady-state conditions [18].

2. Risk factors for insulin resistance

A number of risk factors are found for insulin resistance, together with being overweight or obese or pursuing a sedentary lifestyle [19]. Numerous genetic constituents can elevate the chances for the same, and there are some particular medical circumstances correlated with insulin resistance [19].

The National Institute of Diabetes and Digestive and Kidney Diseases has specified several hazard factors:

1. Age of 45 or more.

2. Native Alaskan, Asian American, American Indian, African American, Native Hawaiian, or Latino/Hispanic ethnicity.

3. Having abnormal health states such as increased systolic/diastolic pressure and increased levels of cholesterol.

4. Having gestational diabetes history.

5. Having a history stroke or heart disease [19].

6. In addition, some medications and other health conditions can raise the risk [19].

2.1 Types of people more likely to develop insulin resistance

Individuals who have hereditary factors or lifestyle-related factors are bound to have in their later life insulin resistance or prediabetes [20]. Hazard factors incorporate:

- Overweight or obesity.

- Age 45 or more.

- Having a parent, sibling, or sister with diabetes.

- African American, Alaskan Native, American Indian, Asian American, Hispanic/Latino, Native Hawaiian, or Pacific Islander American ethnicity.

- Physical idleness.

- Health conditions, for example, hypertension and high cholesterol levels.

- A history of gestational diabetes.

- A history of coronary illness or stroke.

- Polycystic ovary disorder, also known as PCOS.

- Individuals who have metabolic disorder—hypertension, irregular cholesterol levels, and enormous waist size—are bound to have prediabetes.

- Hormonal imbalances, for example, Cushing's disorder and acromegaly.

- Sleep issues, particularly rest apnea.

In spite of the fact that you cannot change hazard factors, for example, family ancestry, age, or ethnicity, you can change lifestyle factors such as eating, physical activity, and weight. These ways of life changes can bring down your odds of creating insulin resistance or prediabetes [21].

There are a number of other hazard factors that are firmly connected to insulin resistance; however, these factors are yet to give clear answers about how much these variables might be a reason for the same.

The variables include:

- Abundance of fat

- Having hypertension or hypercholesterolemia

- Having a nearby relative with type 2 diabetes

- History of gestational diabetes

- Having potential to develop type 2 diabetes

2.2 Diet

The food that we take are regularly seen as a conspicuous reason for diabetes and frequently supposed as a reason.

Many studies have shown that our diet can have an effect in type 2 diabetes; however, it is one factor among numerous others, and speculations ought not be drawn without the thought of other contributing variables.

2.3 Contributions of genetics

Research has revealed various factors, which are related with an elevated danger of diabetes. There are various elements which can impact our plasma glucose, as

well as taking into consideration where we disperse fat in our body and how efficiently our muscles allow glucose to enter from the blood.

It is a well-known fact that genes help control and regulate every metabolic activity in the body, and mutations, in genes, which have influence in the digestion and absorption process can cause problem with controlling blood glucose level. To date scientists have distinguished more than 60 genes related with type 2 diabetes mellitus (T2DM).

2.4 Medication

Corticosteroids treat mainly inflammatory disorders, as rheumatoid joint inflammation, lupus, and hypersensitivities. Normal steroids incorporate hydrocortisone and prednisone. Be that as it may, steroid creams (for a rash) or inhalers (for asthma) aren't an issue.

Medications that treat nervousness, attention deficit hyperactivity disorder (ADHD), sorrow, and other emotional well-being issues can incorporate clozapine, olanzapine, risperidone, and quetiapine:

- Contraception pills

- Medications that treat hypertension, for example, beta-blockers and thiazide diuretics

- Statins to bring down cholesterol

- Adrenaline for serious hypersensitive responses

- High doses of asthma medications or medications that you infuse for asthma treatment

- Isotretinoin for skin breakout

- Tacrolimus, which you get after an organ transplant

- A few meds that treat *human immunodeficiency virus* (HIV) and hepatitis

- Pseudoephedrine, a decongestant in some cold and influenza prescriptions

- Niacin or vitamin B3

Alongside these hazard factors, different things that may add to insulin resistance incorporate:

- Antihypertensive agents such as β-blockers, diuretics, oral contraceptives, corticosteroids, nicotinic acid, and antipsychotic agents are said to increase insulin resistance [22, 23]; in addition, many anti-retroviral protease inhibitors utilized to treat human immunodeficiency virus infection also cause insulin resistance. The mechanisms of actions vary: β-blockers impede the secretion of insulin from the pancreas by blocking the β-adrenoceptors, depletion of the blood levels of potassium is the main action of thiazide diuretics, counter-regulatory hormonal activity is the main action of oral contraceptives and corticosteroids, and loss of peripheral subcutaneous fat with partial

lipodystrophy (with resultant accumulation of truncal adipose tissue) is the main action of HIV-1 protease inhibitors. All these ultimately lead to insulin resistance [24].

2.5 Lifestyle factors

Many hormones can instigate insulin resistance, prominent among them being human placental lactogen, growth hormone, and cortisol [25]. Counteraction of insulin is done by cortisol and can cause elevated hepatic gluconeogenesis, decreasing peripheral use of glucose and elevating insulin resistance [26]. Cortisol does this by diminishing the translocation of glucose transporters (especially GLUT4) to the respective cell membrane [27, 28]. This is based on the noteworthy augmentation in the sensitivity of insulin in humans after doing bariatric surgery and surgical removal of the duodenum in rats [29]; it has been speculated that some substance is manufactured in the mucosa of duodenum, which gives a signal to the body cells to become insulin resistant. With removal of the producing tissue, cessation of the signal occurs, and reverting back of the body cells to normal insulin sensitivity is seen. No such particular substance has been discovered as yet, and the certainty of such a substance remains speculative. Leptin is a hormone derived from the adipocytes and ob gene [30] whose role is the regulation of hunger by forewarning the body when it is full [31]. Researches have depicted that dearth of leptin leads to severe obesity and is intensely associated with insulin resistance [32].

3. Pathogenesis

Four major metabolic abnormalities characterize type 2 diabetes mellitus: impaired insulin action, obesity, increased endogenous glucose output, and insulin secretory dysfunction [33–35]. In spite of the fact that there is considerable authentication that three of these idiosyncrasies exist in most people before the commencement of diabetes, the concatenation with which they evolve and their corresponding contributions to the advancement from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT), and ultimately to type 2 diabetes [36–38], cannot be confirmed for sure even though some detailed longitudinal studies have provided some information [39–44]. Contemporaneous comprehension of the pathogenesis of type 2 diabetes is established on a wide-reaching number of cross-sectional [45–57] and prospective [58–72] studies. The evolution (and subsequent progress) of type 2 diabetes mellitus is delineated by a gradual degeneration of glucose tolerance over several years [33–38]. Prospective and cross-sectional data demonstrate that defects in insulin secretion, body weight gain, insulin action, and an elevation in endogenous glucose output are cardinal in this decline [45–56]. The pathogenetic history of diabetes—the corporeal chain of events with which these metabolic aberrations evolve in relation to one another throughout the various stages of the illness—remains unrevealed. Many authors have suggested that a flaw in insulin activity is the principal aberration in the premature stages of the evolution of type 2 diabetes and that secretory dysfunction of insulin takes place only at a later stage.

3.1 Molecular mechanism of insulin resistance in the muscle

Cellular contents of lipids inside myocytes (of muscles) are referred to as intramyocellular lipid (IMCL) and basically reflect intramyocellular triglyceride content. Although IMCL emphatically relates with muscle insulin resistance in

inactive people, triglycerides themselves have been disassociated from insulin resistance, recommending that other lipids (e.g., diacylglycerols, ceramides, and so on) intervene insulin resistance [73]. Various investigations have depicted the interrelationship insulin resistance in muscles and between diacylglycerol (DAG) content. Insulin-animated tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1) and IRS-1-related phospho-inositide 3-kinase (PI3K) actuation were intensely debilitated in skeletal muscle of lipid-injected people [74] and rodents [75, 76]. In rodents, lipids and high-fat intake bring about transient increments in muscle DAG content [75], bringing about continued appearance of protein kinase C-theta (PKCθ) that constrained phosphorylation of IRS-1 by insulin receptor substrate 1 (IRTK). Lipid mixtures in normal human volunteers correspondingly elevated skeletal muscle DAG [77, 78] and caused muscle insulin resistance. The improvement of muscle insulin resistance can prompt metabolic ailment. This has been seen in hereditary mouse models of particular muscle insulin resistance [79], which are inclined to hepatic steatosis [75] and increased adiposity [77]. In young, lean, and people with skeletal muscle insulin resistance, ingested glucose is not taken up by muscle and gets occupied to the liver, where it becomes substrate for liver once more by lipogenesis, increasing liver triglyceride; furthermore, plasma triglyceride increase results in decreasing plasma high-density lipoprotein (HDL) levels [80]. Nonalcoholic fatty liver disease (NAFLD) is unequivocally connected with hepatic insulin resistance. In patients with lipodystrophy, ectopic lipid accumulation in the liver and skeletal muscle was related with extreme hepatic and muscle insulin resistance [81]. Leptin treatment diminished the consumption of calorie, settled hepatic steatosis, and improved insulin activity [82]. Lipodystrophic mice have a comparable phenotype, and fat transplantation protected these mice by permitting redistribution of lipids from ectopic destinations to transplanted fat tissue and standardization of insulin activity [83]. Mice overexpressing lipoprotein lipase in the liver cause hepatic steatosis and liver-explicit insulin resistance [84]. In rodents and mice, high-fat eating regimens lead to hepatic steatosis and hepatic insulin resistance. In this way, these considerations show that ectopic lipid in the liver is explicitly related with hepatic insulin resistance. Magkos et al. showed that hepatic DAG content (not hepatic ceramide content) was the best indicator of hepatic insulin resistance in obese people [85]. There are a few conditions wherein hepatic steatosis shows up disassociated from hepatic insulin resistance. A typical single-nucleotide polymorphism (rs738409, I48M) in the lipid bead protein-like phospholipase domain-containing protein 3 [patatin-like phospholipase domain-containing A3 gene (PNPLA3), likewise called adiponutrin (ADPN)] has been related with expanded hepatic steatosis, but not insulin resistance [86–88]. Along these lines, occasions of obvious disassociation of hepatic steatosis and hepatic insulin opposition might be clarified by a superior comprehension of the subcellular conveyance of DAG [89]. Ceramides are additionally bioactive lipid particles that are embroiled in the advancement of insulin resistance. Increments in hepatic and muscle ceramide content have been related with insulin resistance in rodents, and inhibitors of ceramide blend can forestall insulin resistance [90, 91]. In any case, a disassociation between ceramide substance and tissue insulin resistance has been revealed in numerous investigations [85, 92, 93], and the fundamental component connecting ceramides to insulin resistance has not been completely finalized. As of late, some investigations analyzed how a particular ceramide species, C16:0, resists mitochondrial oxidation, permitting triglyceride to accumulate and cause insulin resistance [94, 95]. Despite the fact it has not been concluded, it is conceivable that the equal relationship between C16:0 ceramide and mitochondrial oxidation could additionally cause increments DAG and impede insulin action.

3.2 Insulin resistance in the adipose tissue

Some of the actions of insulin on adipose tissue are (1) stimulation of uptake of glucose and biosynthesis of triglyceride and (2) suppression of triglyceride hydrolysis-cum release of free fatty acids (FFA) and glycerol into the blood [96, 97]. It has been seen that adipose tissue insulin resistance (Adipo-IR), which means diminished suppression of lipolysis when high insulin levels are present, is interlinked with glucose intolerance, and increased plasma FFA amounts have also shown to diminish insulin signaling in muscles, endorse gluconeogenesis in the liver, and diminish glucose-activated insulin response [97–103]. In spite of the fact that the natural history and role of β-cell abnormality (or impairment) and insulin resistance in muscle are firmly established in the evolution of T2DM, the influence of Adipo-IR in the progression from normal glucose tolerance (NGT) to type 2 diabetes mellitus (T2DM) is still not clear. It is possible to quantitate palmitate turnover by the utilization of tracers [104–106] which can also provide the release rate of glycerol [107, 108] to furnish a lipolysis index. Tracer turnover (i.e., labeled palmitate or glycerol) or FFA suppression during insulin infusion (euglycemic-hyperinsulinemic clamp) or oral glucose tolerance test (OGTT) has led to the development of a number of indices of Adipo-IR [109]. Gastaldelli et al. [104] *confirmed that* fasting Adipo-IR index can be considered as a reliable index of insulin resistance in the fat cell when considered over the entire spectrum from NGT to T2DM. There has been consistent demonstration of weakened suppression of plasma FFA and also glycerol and 14C-palmitate turnover with the stepped hyperinsulinemic clamp [106, 110, 111] (i.e., adipocyte insulin resistance) in persons having T2DM. Therefore a decline in insulin secretion/insulin resistance (disposition) index has been seen with progression from lean NGT to obese NGT to IGT [112]. A decline in the secretion from β-cell of insulin is also interlinked with an elevation in the fasting Adipo-IR. Therefore, it can be said that the fasting adipocyte insulin resistance index (fasting FFA × fasting insulin) increases in a forward-looking, innovative manner over the stretch of glucose tolerance, extending from NGT to T2DM, and furnishes a reliable index of fat cell sensitivity to the actions of insulin [113–115]. In contradiction, there is increment of adipocyte insulin resistance index during OGTT (from NGT to IGT) and decrease with advancement of IGT to T2DM; this is due to gradual deficiency of the secretion of insulin in this group having diabetes. In conclusion, the gradual decrease in β-cell function that progresses from NGT is interlinked with a gradual elevation in fasting Adipo-IR and FFA [104].

Fat insulin resistance is the failure of insulin to activate fat glucose transport, advance lipid take-up, and diminish lipolysis. While diminished fat glucose take-up is exhibited in both in vivo and in vitro models, metabolic effect of hindered insulin-intervened glucose take-up in fat tissue is not well explained. For instance, the loss of fat GLUT4 in mice does not modify adiposity or, on the other hand, how weight gain prompts insulin resistance in skeletal muscle and liver [116]. Glucose transport into fat cells initiates starch reaction component restricting protein (ChREBP), which may affect fat lipid digestion [117]. Adipocytes discharge explicit unsaturated fats that are related with increased insulin affectability, as palmitoleate [118, 119] or monomethyl chain unsaturated fats [120].

4. Methods for diagnosis

4.1 Fasting insulin levels

A fasting serum insulin amount of more than 25 mU/L or in other sense 174 pmol/L designates insulin resistance. The same amounts pertain to 3 hours after taking the last meal [121].

4.2 Glucose tolerance testing

While performing a glucose tolerance test (GTT), a patient who is fasting is given a 75 g of glucose orally. Then plasma glucose levels are continuously monitored (along with urine glucose) for a period of 2 hours.

The elucidation of the test is established on the guidelines of the World Health Organization (WHO). After a period of 2 hours, a plasma glucose amount of less than 7.8 mmol/L (140 mg/dL) is regarded as normal, and a plasma glucose amount of between 7.8 and 11.0 mmol/L (140 to 197 mg/dL) is regarded as impaired glucose tolerance (IGT), and a plasma glucose amount of greater than or equal to 11.1 mmol/L (200 mg/dL) is regarded as diabetes mellitus. Extension of the testing (for several more hours) may reveal a hypoglycemic "dip" that is a result of an overshoot in insulin production after the failure of the physiologic postprandial insulin response.

4.3 Using the hyperinsulinemic euglycemic clamp

"Hyperinsulinemic euglycemic clamp" is also known as the gold standard for investigating and quantifying insulin resistance. It is so-called because it calculates the level of glucose obligatory to reimburse for an elevated insulin level without giving rise to hypoglycemia [122]. It is a kind of glucose clamping technique. The test is seldom carried out in clinical settings but is utilized in medical research [123]. The process takes around 2 hours. Insulin is infused through a peripheral vein. The rate is of infusion is 10–120 mU per m^2/minute. With the intention to recompense for the infusion of insulin, 20% glucose is infused to sustain blood glucose levels between 5 and 5.5 mmol/L. The blood sugar levels every 5 to 10 minutes, to determine the rate of infusion of glucose [123]. The determination of insulin sensitivity is made by the rate of glucose infusion in the last 30 minutes of the test. If greater levels (7.5 mg/min or greater) are required, the patient is considered as insulin sensitive. Low levels such as 4.0 mg/min or lower than that designates that the body is resistant to actions of insulin. Levels between 4.0 and 7.5 mg/min are not conclusive and indicate "impaired glucose tolerance," which is a premature gesticulation of insulin resistance [123, 127]. This basic method may be modified significantly by the utilization of glucose tracers.

4.4 Modified insulin suppression test

Gerald Reaven developed the modified insulin suppression test at Stanford University. The test corresponds well with the euglycemic clamp, with minute operator-dependent error. Particularly, this test has been utilized in research correlating to the metabolic syndrome [123]. A 25 μg of octreotide (Sandostatin) is given to the patient in 5 mL of normal saline over a period of 3–5 minutes through intravenous infusion (IV) as a primary bolus. Subsequently, the patient is continuously infused with an IV infusion of somatostatin (0.27 μg/m^2/min) to repress internal glucose and insulin secretion. Next, 20% glucose and insulin are infused at varying rates of 32 and 267 mg/m^2/min. Plasma glucose is monitored at 0, 30, 60, 90 minutes, and lastly at 120 minutes and subsequently after each 10 minutes for the final 30 minutes of the study. The averages of these final four values are utilized to ascertain the steady-state plasma glucose level (SSPG). People having an SSPG greater than 150 mg/dL are contemplated to have insulin resistance [45].

4.5 Homeostatic model assessment (HOMA)

By this method it is possible to quantify insulin resistance. Also, pancreatic beta-cell function can be possibly elucidated:

$$\text{HOMA-IR} = \frac{\text{Glucose} \times \text{Insulin}}{22.5} \tag{1}$$

and

$$\text{HOMA-}\beta = \frac{20 \times \text{Insulin}}{\text{Glucose} - 3.5\%} \tag{2}$$

where glucose is in mmol/L.
Also,

$$\text{HOMA-IR} = \frac{\text{Glucose} \times \text{Insulin \%}}{405} \tag{3}$$

and

$$\text{HOMA-}\beta = \frac{360 \times \text{Insulin \%}}{\text{Glucose} - 63} \tag{4}$$

where glucose is in mg/dL.

Note: insulin is taken in μU/mL; both glucose and insulin are taken during fasting; IR means insulin resistance; HOMA-β is the percentage of beta cell function [124–128].

4.6 Quantitative insulin sensitivity check index (QUICKI) method for insulin assessment

QUICKI is obtained utilizing the inverse of the addition of the logarithms of the fasting insulin and fasting glucose:

$$1/[\log{(\textit{fasting insulin } \mu U/mL)} + \log{(\textit{fasting glucose } mg/dL)}] \tag{5}$$

The QUICKI method corresponds well with glucose clamp researches (r = 0.78) and is very good for the measurement of insulin sensitivity (IS), which is derived by utilizing the reciprocal quantity of insulin resistance (IR).

5. Conclusions

From the time insulin resistance was discovered, the cellular and molecular mechanisms were the considerations for which drugs were tried for diabetes mellitus. Considering the cellular mechanisms of insulin resistance which are mostly concerned with plasma cell membrane glycoprotein-1 (PC-1), also termed as ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), the mechanism is really complex. The full understanding of the cellular mechanisms will permit the development of novel targets for various treatment modalities. From the therapeutic point of view, we need to have a clear knowledge about the cellular mechanism of insulin resistance in order to treat and also to prevent the occurrence of diabetes from prediabetic stage. From recent studies, it is evident that insulin resistance can be stopped or reversed if the pathophysiology is clear. It is the necessity to implement a huge global strategic plan for identifying and preventing/treatment of insulin resistance in the prediabetic stage.

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